

Sudden Cardiovascular Death Associated with Supplement Use in the Young

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Introduction

- ◆ Sudden cardiac death in young adults is rare, but remains a highly litigious and emotionally charged topic.
- ◆ Evaluation is complicated by the presence of normal physiologic adaptations of cardiac anatomy at autopsy.
- ◆ In young adults, up to 35% of non-traumatic deaths do not have a clear etiology despite autopsy.
- ◆ Herbal supplements have been suggested as one possible mechanism of predisposition for arrhythmic sudden cardiac death.

Eckart RE, et al. *Ann Intern Med* 2004;141:829-34
Maron BJ. *N Engl J Med* 2003;349:1064-75

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Herbal Supplements

- ◆ Prominent in this field is *Ephedra sinica*
 - ◆ Ma huang
 - ◆ Used for treatment of asthma, the common cold, and as a stimulant.
 - ◆ Widespread use in the US initially in the 1920's
 - ◆ Again, used as decongestants and CNS stimulants
 - ◆ In the last 20 years, Ephedra gained popularity again
 - ◆ Now for weight loss and as an energy supplement
- ◆ In 2001, 17.8 Billion dollars spent on supplements in the US
- ◆ In 2001, Ephedra containing products accounted for 64% of all adverse reactions to herbs in the US, while representing <1% of all herbal products sold.

AHRO Publication No. 03-E022. February 2003
Bent S, et al. Ann Intern Med 2003;138:468-71

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Known Physiologic Effects

- ◆ Increases blood pressure, heart rate, cardiac output, peripheral vascular resistance
- ◆ Metabolife 356 was used by ~12 million Americans in 2002.
 - ◆ 15 healthy young volunteers using Metabolife 356
 - ◆ Increased systolic blood pressure and stroke index
 - ◆ QTc was prolonged a mean of 27 msec
 - ◆ For purposes of drug approval, the FDA considers an absolute QTc of 450, 480, and 500, or a relative increase of 30 and 60 msec to represent escalating risk.
- ◆ In animal models, ephedrine supplements in standard over the counter dosing increase ischemia dependent ventricular arrhythmias.

Dhar R, et al. *Mayo Clin Proc* 2005;80:1307-15
Marcus DM, et al. *N Engl J Med* 2002;347:2073-6
McBride BF, et al. *JAMA* 2004;291:216-21
Adamson PB, et al. *J Am Coll Cardiol* 2004;44:1675-8

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Risk : Benefit Ratio

- ♦ FDA regulation?
- ♦ FDA adverse event reports
 - ♦ 87 adverse events associated with ephedra
 - ♦ 10 deaths -- 47% secondary to cardiovascular cause
 - ♦ 926 cases of possible Ma Huang toxicity
 - ♦ 37 patients with stroke, myocardial infarction, or sudden cardiac death
- ♦ In Denmark, ephedrine/caffiene supplements are a prescription product
 - ♦ 250,000 patients
 - ♦ No increase in cardiovascular events

Haller CA, Benowitz NL. *N Engl J Med* 2000;343:1833-8
Samenuk D, et al. *Mayo Clin Proc* 2002;77:12-6
Hallas J, et al. *Am J Epidemiol* 2008;168:966-73

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Can this *really* be healthy . . . ?



Found in the bunk of a U.S. Army Soldier in Iraq
with unexpected non-traumatic death . . .

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Study Design

- ◆ We hypothesize that herbal supplementation, and specifically ephedra, are temporally related to idiopathic sudden cardiac death in the military population.
- ◆ Review of non-traumatic sudden death within the Department of Defense with an available clinical record or autopsy for adjudication as to the cause of death.
- ◆ Sponsored by the Air Force Medical Research Program (AF/SGRS).

Defining the Cohort

- ◆ 1,044 non-traumatic deaths suspected to be cardiac or idiopathic identified from 1998 to 2008.
 - ◆ 51 (5.1%) subjects excluded for lack of clinical history or autopsy
 - ◆ 130 (12.5%) subjects excluded for unavailability of records
 - ◆ 12 (1.2%) subjects excluded for clear non-cardiac etiology
- ◆ 902 subjects with available records and clinical history or autopsy form the basis of the cohort.

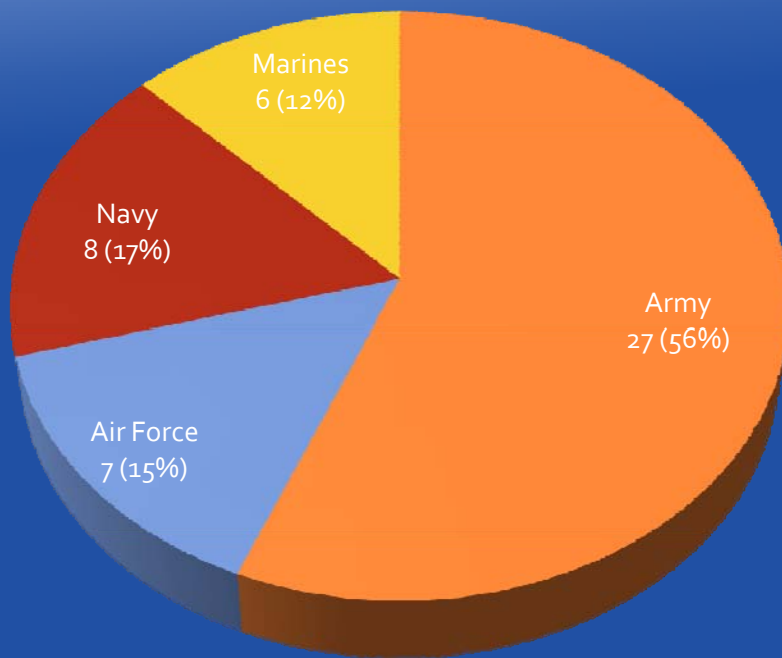
Results

- ◆ 48 subjects identified with toxicologic or reported use of substances of interest.
 - ◆ Mean age 34 ± 10 years
 - ◆ Gender – male 44, 91.7%
 - ◆ Race
 - ◆ Caucasian (33, 68.8%)
 - ◆ African-American (11, 22.9%)
 - ◆ Asian (1, 2.1%)

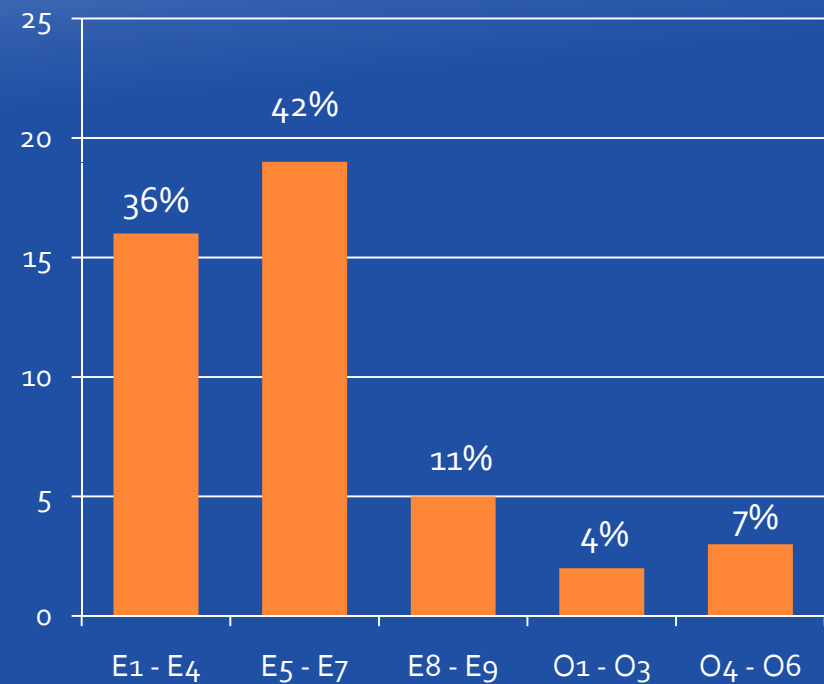
Baseline Characteristics

Military Specific Findings

Branch



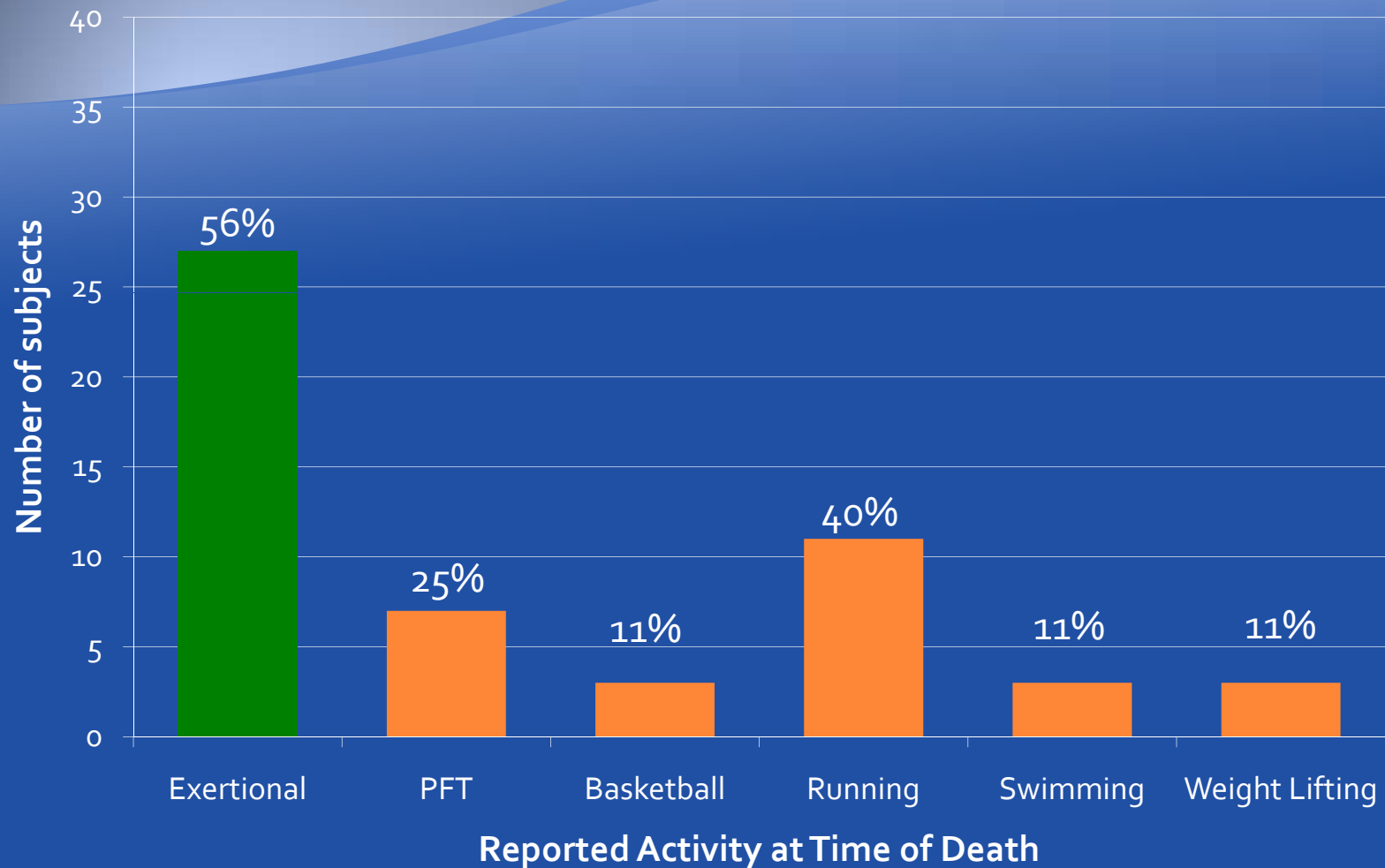
Pay Grade



Use of Supplements

- ◆ Thermogenic agents – 34 (70.1%)
 - ◆ Diet Fuel, Ripped Fuel, VigorPlex, Xtreme Lean, etc.
- ◆ Clinical or toxicologic ephedrine or phenylpropanolamine – 28 (58.3%)
- ◆ Negative toxicology findings – 23 (47.9%)

Activity at Time of Death



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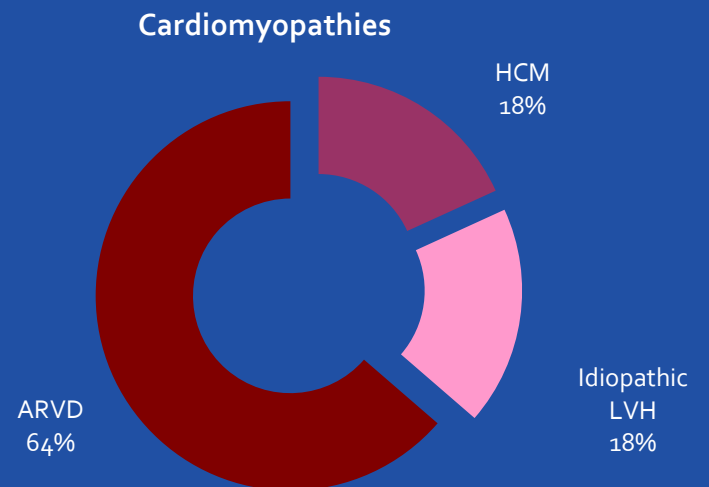
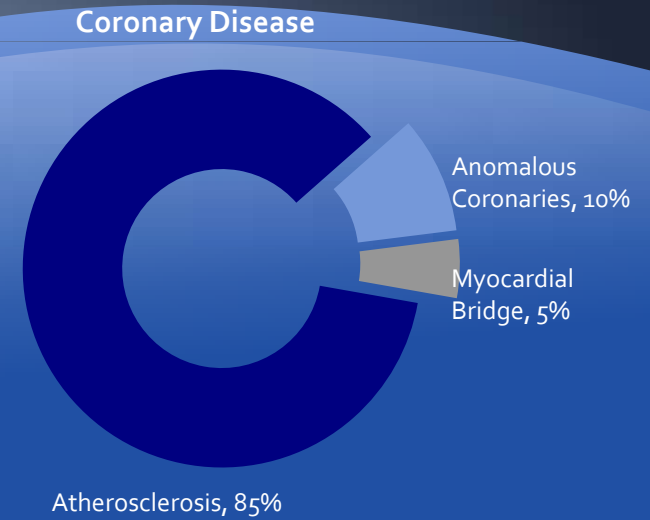
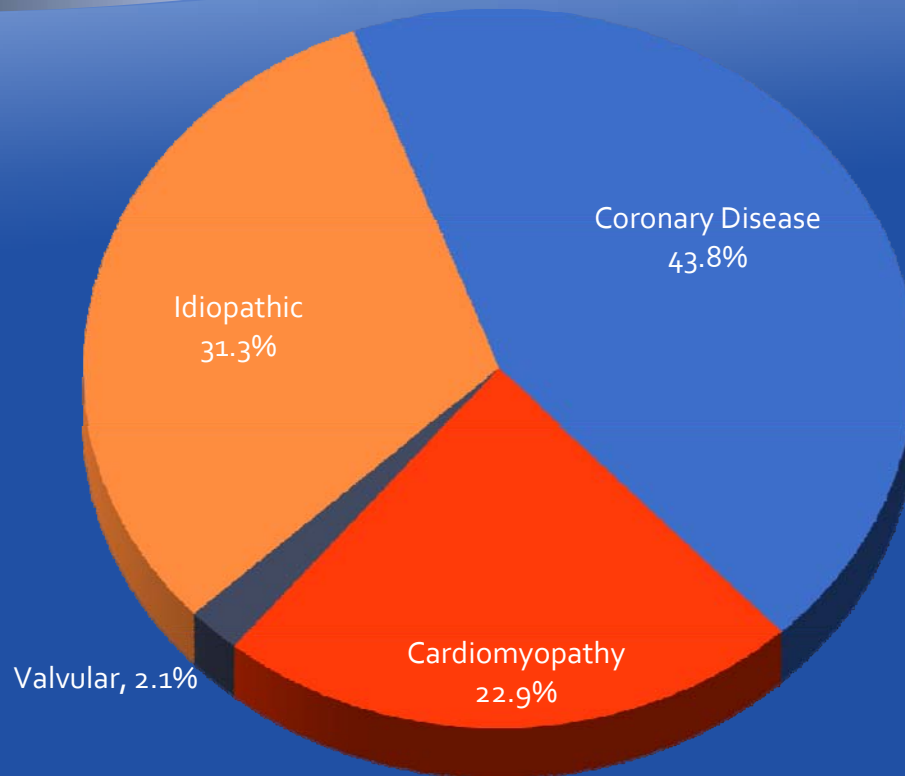
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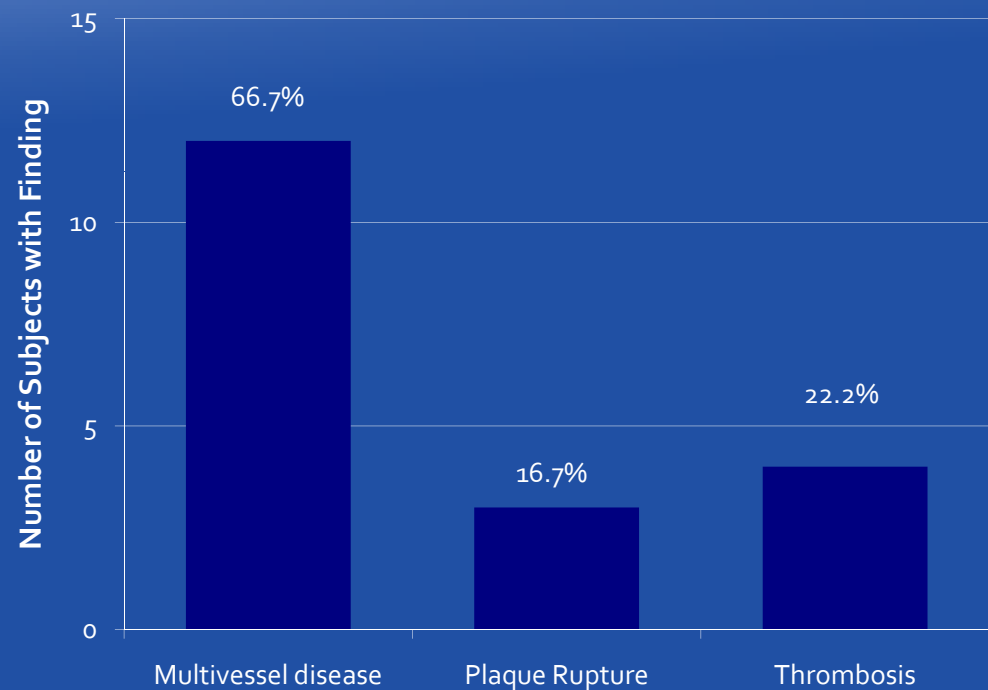
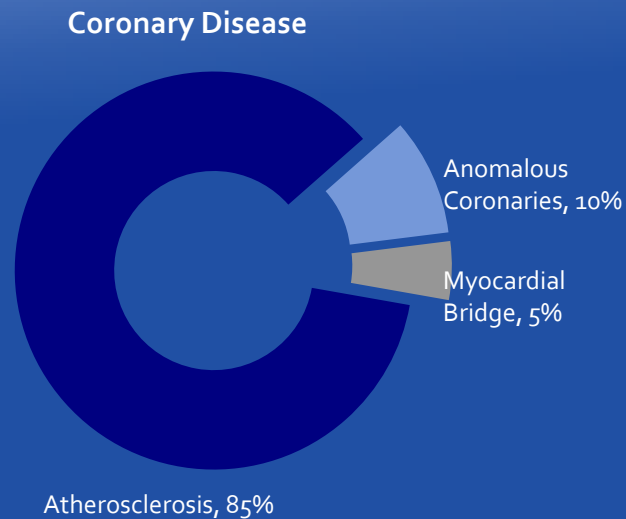
Antemortem Scenario

- ♦ Reported prodrome 16 (33.3%)
 - ♦ Chest pain (n=7)
 - ♦ Syncope or palpitations (n=4)
 - ♦ Dyspnea (n=3)
 - ♦ Seizure (n=1)
- ♦ Location of death
 - ♦ Out of hospital 15 (31.3%)
 - ♦ Emergency Department 27 (56.3%)
 - ♦ In hospital 3 (6.3%)

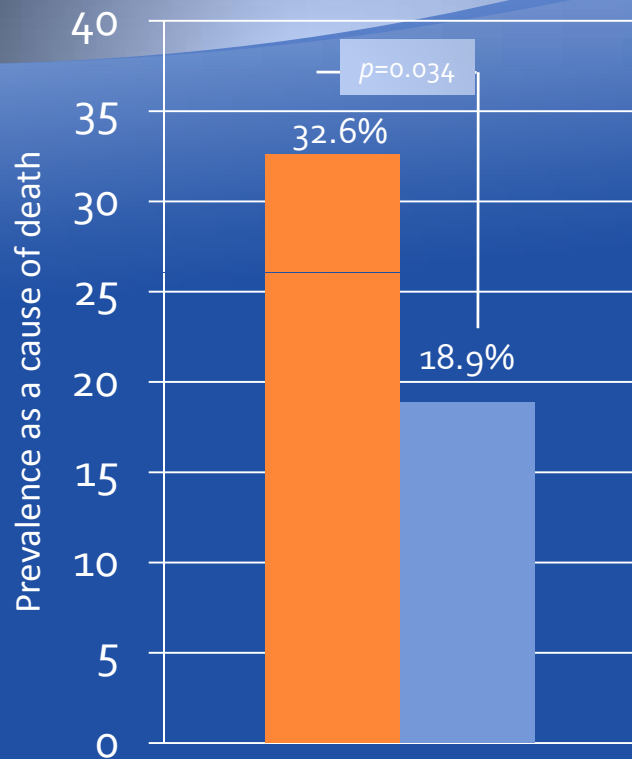
Cause of Death



Findings on Autopsy of those with Death due to Atherosclerosis



Prevalence of idiopathic sudden cardiac death



Supplement use (n=48)
No known supplement use (n=854)

Age at time of death stratified by use of supplements



Context of Findings

- ◆ Previous case reports of sudden death temporally associated with supplement use may be anecdotal.
- ◆ Case ascertainment bias limits the ability to identify high risk characteristics of 'at risk' individuals.
- ◆ Testing bias may not identify those older, senior personnel who may also be using supplements.

Conclusion

- ◆ Supplement use has an anecdotally skewed risk:benefit ratio
- ◆ The aforementioned limitations may limit generalizability.
- ◆ Health care providers must query about intake of supplements and assess for abuse across all ages and ranks.

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